MEDICAL SCIENCES

INFLUENZA. CLINICAL COURSE, DIAGNOSTICS, TREATMENT AND PREVENTION

Dr. Abdulhamid Ali Kahtan
D.M., pediatrician and pediatric pulmonologist at the pediatric department, multidisciplinary hospital for active treatment "Uni Hospital" - city of Panagyurishte, Bulgaria
https://doi.org/10.5281/zenodo.14499254

Abstract
Influenza is an infectious disease caused by RNA viruses and is the leading cause of morbidity and mortality worldwide. Influenza viruses are unique among respiratory viruses in their antigenic variability, which allows them to "evade" human immune defenses, and is also the main cause of epidemics, which necessitates the annual development of new influenza vaccines against new circulating strains. It is the phenomenon of antigenic variation that explains why influenza continues to be the main epidemic disease of humanity. Despite the enormous progress in the study of this infection in scientific and theoretical terms, it continues to pose extremely serious problems for public health. And in this regard, recently, the infection of humans with the bird virus influenza A (H5N1), has increased the danger of the emergence of an influenza virus with pandemic potential, which on the one hand confirms the need for vaccine prophylaxis, knowledge of the clinical course of the manifestation, its complications and on the other hand shows the importance of rapid diagnosis and timely administration of specific anti influenza medications, the best therapeutic effect of which is achieved when administered within the first 48 hours of the onset of symptoms.

Keywords: influenza, complications, vaccine prophylaxis, rt - PCR, ICM.

Influenza viruses that infect humans are classified into three main types: type A, type B, and type C. Influenza viruses type A and B are the main influenza pathogens and cause epidemic diseases in humans. Influenza type C is mainly a sporadic cause of upper respiratory tract disease (URD). There are significant differences in genetic organization, structure, host range, epidemiology, and clinical features among the three types of influenza viruses. Influenza type A viruses are divided into subtypes based on the surface hemagglutinin (H) and neuraminidase (N) antigens. Influenza A has 16 different H subtypes and 9 different N subtypes, of which only H1, H2, H3, H5, N1, and N2 are associated with human influenza epidemics. Influenza occurs in annual outbreaks, seasonal epidemics, and pandemics. These categories differ in the number of cases. The reason for this epidemiological picture lies in the ability of the influenza virus to change its antigenic properties and "evade" the human immune defense. Epidemics are due to the so-called antigenic drift, a phenomenon associated with a gradual and relatively continuous change in the viral H and N antigens. Pandemics are due to the so-called antigenic shift, a phenomenon associated with the occurrence of sudden changes in one or two genetic segments during the replication of two different viruses (human and avian) in a given cell, and this leads to the emergence of a new virus.[2][3][4][5][7][9]

The source of infection with influenza is asymptomatic infected individuals, sick people, sick birds, healthy birds carrying the virus, and sick mammals. However, the main source of infection in humans is a sick person. It secretes the virus in the last 1-2 hours of the incubation period and 1-3, maximum 5 days from the onset of clinical manifestations. Influenza is transmitted by airborne droplets, and close contact between people is of great importance for this transmission mechanism. Effective transmission of the avian influenza virus A (H5N1) from person to person has not been observed so far and is transmitted only by direct contact with sick or infected birds. Children from 6 months to 3 years of age are most susceptible to influenza.

[9][17][21]

Clinical course of influenza.

Typical uncomplicated influenza, after a short incubation period of 1 to 2 days, begins with a sudden onset of symptoms with a picture of toxicinfectious syndrome, including chills, high fever, severe headache, severe general malaise, muscle aches, anorexia, often accompanied by dry cough, flushed face, injection and tearing of the eyes, runny nose, stuffy nose and sore throat, these respiratory symptoms appear 1-2 days after the onset of the disease.[2][3][7][9][15]

Children, especially those under 3 years of age, have a higher incidence of gastrointestinal manifestations, such as vomiting, diarrhea and abdominal pain, with diarrheal syndrome being more common in influenza type B, but according to literature data it also occurs in "bird flu" A (H5N1).[1][24][25]

In the initial stages of infection, due to inflammatory changes in the URT, a number of proinflammatory cytokines (IFN,IL-1,TNF-α) are released, which cause the early toxicoinfectious syndrome. The massive immune response can cause a life-threatening cytokine "storm" as a result of massive viral replication. This effect is assumed to be the cause of the unusually high mortality from the highly pathogenic avian influenza virus A (H5N1) commonly called "bird flu" and the pandemic strain of 1918(Spanish flu).[2][3][4][7][9][15][16][22]

Clinical forms of influenza.

a. Mild. Short-term and mild course, with subfebrile or afebrile fever, and weakly manifested or absent

symptoms of intoxication. Recovery usually occurs in 4 - 5 days.

b. Moderate. Typical course, the main symptoms and syndromes are present, without extreme deviations in the clinical and paraclinical picture.

c. Severe with a violent onset, severe intoxication, hemodynamic and hemostatic disorders

d. Fulminant. Very high fever above 40 °C, unbearable headache, weakness, loss of appetite, acute hemodynamic collapse, convulsions, loss of consciousness. Death usually occurs in 1-2 days.[2][4][8]

Complications of influenza.

Complications of influenza occur most often in people with risk factors, namely age > 65 years, children under 2 years old (especially infants) and in people with chronic diseases, pregnant women in the 2nd and 3rd trimesters and in children with concomitant diseases (congenital and acquired heart defects, cardiomyopathies, bronchopulmonary dysplasia, asthma, cystic fibrosis, diabetes mellitus and neuromuscular diseases affecting the accessory muscles of respiration). According to literature data, "bird flu" A(H5N1) is associated with a high incidence of pneumonia (> 50%), and deaths have been associated with multisystem involvement, including CNS complications, heart and kidney failure. During the clinical course of influenza, various complications may develop, caused mainly by the influenza virus or secondarily, most often by bacterial superinfection. Complications of influenza are: respiratory and non-respiratory. Respiratory complications are primary and secondary. Primary complications usually occur within the first 1-4 days, at the beginning of the disease, in severe and fulminant forms and include interstitial pneumonia with a serious prognosis, with high mortality. In children, the primary complication of influenza can be stenosing laryngotracheobronchitis(croup). Secondary respiratory complications include secondary bacterial pneumonia, sinusitis, otitis media and exacerbation of chronic bronchitis, bronchial asthma and cystic fibrosis. Extrapulmonary complications include: acute myositis, pericarditis, myocarditis, toxic shock syndrome, Reye's syndrome and CNS complications (influenza serous meningitis, primary meningoencephalitis and encephalitis, cerebral edema, transverse myelitis, myelopolyradiculoneuritis, isolated neuritis, polyneuritis and Guillain-Barré syndrome).[18][26][27][30]

Differential diagnosis.

First of all, differential diagnosis should be made with acute respiratory diseases (ARDs), which are occurring in the form of catarrhal changes in the upper respiratory tract (URT), caused by a heterogeneous group of viruses called respiratory viruses (adenoviruses; rhinoviruses, parainfluenza viruses, coronaviruses, respiratory syncytial virus and others). Clinically, it is difficult to distinguish ARDs and influenza in the early stages. In the case of ARDs, intoxication manifestations are less pronounced and their onset is not as acute as in influenza. Catarrhal syndrome in influenza appears 1-2 days later and is less pronounced. ARDs can also be caused by bacteria such as group A B-hemolytic streptococci. In the latter case, the positive result of the rapid antigen test, the isolation of a bacterium in the microbiological examination of throat secretions or increased serum AST levels make the diagnosis. Of decisive diagnostic importance is also the localization of the pathological process. Rhinoviruses cause anterior rhinitis, parainfluenza viruses occur with a picture of laryngitis, in young children occurs with a pseudocroup pattern, with a dry, barking cough, inspiratory stridor and difficulty breathing. Adenovirus infection occurs with the characteristic triad (pharyngitis, conjunctivitis and lymphadenitis). RSV viruses cause tracheobronchitis with obstructive syndrome, bronchiolitis or pneumonia in infancy.

Diagnosis of influenza.

The diagnosis of influenza is made on the basis of epidemiological data and characteristic clinical manifestations and etiologically using a number of laboratory methods.

 Paraclinical studies. Characteristic changes in the blood count in viral infections range from mild leukocytosis to leukopenia. CRP and ESR in viral infections usually remain normal, reduced or slightly increased. Laboratory abnormalities characteristic of avian virus A (H5N1) include significant lymphopenia and leukopenia, mild to moderate thrombocytopenia, and elevated transaminase levels, which are poor prognostic signs. In complicated forms, chest and heart radiography, CAT or MRI of the head are performed in CNS complications.

 Rapid diagnostic methods. Various methods are used for rapid diagnosis of influenza. The most widely used tests are based on immunological detection of viral antigen in respiratory secretions.[6][15][42]

The most commonly used rapid diagnostic methods for influenza are:

• Immunochromatographic method (ICM) for rapid diagnosis of influenza. The most widely used immunochromatographic tests for rapid diagnosis of influenza are based on immunological detection of viral antigen in a sample of nasopharyngeal or nasal wash, lavage or aspirate or throat swab. For influenza, these tests include Directigen Flu A + B, Flu OIA (flu optical immunoassay) and QuickVue Influenza A + B test and others.The result is obtained within 15 min. Coincidence of results in influenza testing by two methods (Directigen Flu A + B and RT-PCR) was observed in 85.7% of cases and 90.5% of ICM samples were negative at 48 hours from the start of specific antiviral treatment.[1]

• Immunofluorescence method (IFM). IFM proves the presence of a specific antigen-antibody reaction through antibodies chemically conjugated with a fluorescent dye - fluorochrome. In the presence of homology, the fluorescent antibodies bind to the fixed viral antigens and, when observed with a fluorescent microscope, the antigens are detected by the bright fluorescence of the fluorescent antibodies bound to them. The result is obtained within 1- 4 hours.

• Enzyme-linked immunosorbent assay (ELISA). "ELISA" or EIA test. The result is obtained within 90 minutes. ELISA detects and counts certain antibodies, antigens, proteins and hormones in samples of body

fluids (blood, plasma, urine, saliva and cerebrospinal fluid).

• Polymerase chain reaction (PCR). The modern PCR methodology exists in two varieties: real-time PCR and reverse transcription PCR (Reverse transcription real time polymerase chain reaction - RT-PCR) and is considered the „gold“ standard for detecting the influenza virus and all other respiratory viruses. The material tested can be nasopharyngeal swab, throat swab, nasopharyngeal or bronchial lavage, nasal or endotracheal aspirate, or sputum. Reverse transcription polymerase chain reaction (RT-PCR) is the most modern and highly sensitive method for detecting even low levels of viral nucleic acids in clinical samples and allows for typing and subtyping of influenza viruses within 1 - 24 hours.[28][31][32][33][34][38][40]

 Other diagnostic methods for influenza.

Serological methods. Serological methods mainly include: virus neutralization reaction, hemagglutination inhibition reaction, complement fixation reaction, which prove the presence of antibodies in the serum of influenza patients against influenza virus antigens. Since most people have encountered influenza viruses, a single serum sample is not sufficient, therefore these diagnostic tests have diagnostic value only when examining duplicate serum samples, the first during the acute phase up to the 3rd day from the onset of the disease and the second during the recovery phase of the disease after the 14th, but not later than the 28th day.

Virus isolation. For isolation of the influenza virus, the material examined can be nasopharyngeal swab, throat swab or nasopharyngeal or bronchial lavage, nasal or endotracheal aspirate, sputum. Over 90% of positive cultures can be detected within 3 days of infection, and the rest from 5 to 7 days.[2][3][4][6][7][15][27][30][36]

Treatment and prevention of influenza.

Treatment of influenza. In mild and uncomplicated cases of influenza, treatment is symptomatic. In severe and complicated cases, etiological treatment with antiviral medications and pathogenetic therapy is applied. Extrapulmonary complications (of the CNS, gastrointestinal, cardiovascular, etc.) in influenza are due to oxidative stress, which is why influenza therapy must necessarily include antioxidants (vitamin E and vitamin C). Another mandatory component is the use of an immunomodulator that stimulates pulmonary immunocytes.

Etiological treatment. Two main classes of antiviral drugs are used against influenza. These are neuraminidase inhibitors and M2 protein inhibitors (amantadine derivatives). This class of drugs is also characterized by the fact that they act specifically only on influenza viruses. They are most effective when treatment is started within the first 48 hours of the onset of symptoms.[1][23][29][41]

 M2 protein inhibitors (amantadine derivatives). These were the first antiviral drugs developed in the 1970s, called amantadine and its derivative rimantadine. They are inhibitors of the M2 ion channel protein of influenza viruses and are used for the prevention and treatment of influenza A, but are ineffective against influenza B, since B viruses do not have M2 proteins.

 Neuraminidase inhibitors. These inhibit the action of the neuraminidase of influenza viruses, are effective against influenza A and B, and include oseltamivir, zanamivir, and peramivir. Oseltamivir is also effective against avian influenza. Breastfeeding mothers should not stop breastfeeding during treatment with oseltamivir and zanamivir.[9][17][22][32]

Vaccination and drug prophylaxis of influenza.

 The influenza vaccine is recommended primarily for at-risk population groups. The minimum period for administering the influenza vaccine is up to one month before the expected influenza epidemic. Vaccines produced for one year may be ineffective the following year, as new strains of the influenza virus emerge. There are two types of influenza vaccines: inactivated and live attenuated. The main differences between inactivated and live attenuated influenza vaccines are that the inactivated vaccine (Vaxigrip Tetra and Influvac Tetra) contains killed virus components, is administered intramuscularly and is approved for adults and children aged ≥ 6 months, does not carry a risk of disease transmission, and children under 9 years of age who have never been vaccinated against influenza require two doses of vaccine with an interval of at least 4 weeks between them. While the live vaccine (Fluenz Tetra) contains viruses that are still capable of limited replication; It is administered intranasally at a dose of 0.1 ml in each nostril and is approved for children 2 to 18 years of age, and also for children who have never been vaccinated against influenza, two doses are administered with an interval of at least 4 weeks. [27] [30] [37] [42] [43]

Antiviral chemoprophylaxis. Antiviral drugs (neuraminidase inhibitors and M2 inhibitors) are also used as means for the prevention of influenza. Antiviral chemoprophylaxis is not a substitute for influenza vaccination and is administered during the influenza season for the prevention of influenza primarily in risk groups and their contacts. Antiviral chemoprophylaxis is usually not recommended if more than 48 hours have passed since contact with an infected person. Antiviral chemoprophylaxis can continue for up to two weeks after vaccination with an inactivated influenza vaccine for persons in a non-institutional environment. Children under 9 years of age need chemoprophylaxis for at least 6 weeks (i.e. at least 4 weeks after the first dose of the vaccine and 2 weeks after the second dose) depending on the duration of the interval between the administration of the two doses of the vaccine. Antiviral chemoprophylaxis should continue for 10 days when influenza is diagnosed in a family member. Exposure prophylaxis with antiviral agents should be continued during and for 7 days after the last known exposure to a person with influenza.[23][41]

Antiviral chemoprophylaxis is indicated in the following at-risk populations: 1. For adults and children ≥ 1 year of age who are at high risk of developing complications from influenza, for whom influenza vaccine is contraindicated, unavailable, or is expected to have low efficacy (e.g., individuals who are significantly immunocompromised) or for whom low clinical efficacy

of influenza vaccine has been documented because circulating strains are antigenically different from vaccine strains. In these groups, the duration of chemoprophylaxis should continue for as long as influenza viruses are circulating in the community during the influenza season. 2. For unvaccinated adults, including healthcare workers, and children ≥ 1 year of age who are in close contact with individuals at high risk of developing complications from influenza during periods of influenza activity. 3. For all residents (vaccinated and unvaccinated) in nursing homes and long-term care institutions where an influenza epidemic is present.

Conclusion. Influenza epidemics represent ongoing risks to global human public health, a fact that confirms the need for vaccine prophylaxis and/or chemoprophylaxis, primarily for risk groups of people. On the other hand, early diagnosis and timely administration of specific antiviral agents leads to a reduction in the severity and duration of symptoms, hospitalizations and prevention of influenza complications and unnecessary antibiotic treatment.

References:

1. Kakhtan A. Influenza - clinical course and rapid diagnosis by applying immunochromatographic method in hospitalized patients. Dissertation 2013.

2. Iliev B., G. Mitev, M. Radev. Influenza. Acute respiratory diseases. In: - Infectology, AI “Prof.M. Drinov”, Sofia 2001, 189 – 198.

3. Popivanova N. Influenza. – In: Infectious diseases. Med. ed. “Raykov”, Plovdiv 2007, 141 – 148 .

4. Tiholova M, I. Mitov, Z. Kalvachev, G. Kamenov. Influenza. – In: Infectious diseases, Med. ed. “ARSO”, Sofia 2008, 13 – 19.

5. Hadzhiolova T., R. Kotseva. Orthomyxoviruses. – In: Clinical Virology. "Medicine and Physical Education", Sofia 2006, 154 – 158.

6. Hadzhilova T. Modern methods for influenza diagnosis and genetic characterization of influenza viruses. Dissertation 2006.

7. Chervenyakova T. Influenza. – In: Infectious diseases, "Medicine and Physical Education", Sofia 2009, 148 -151.

8. Chervenyakova T., D. Strashimirov. Influenza. In: Treatment of infectious diseases. "Medicine and Physical Education". Sofia 2011. 140 – 144

9. Plochev K. "Bird flu to humans". Monograph, ed. "Irita" - Sofia 2006

10. Greenhalgh T, Koh GCH & Car J. COVID-19: a remote assessment in primary care. BMJ 2020;368:m1182. doi: 10.1136/bmj.m1182

11. NHS inform. Common cold. 2020. Available at: https://www.nhsinform.scot/illnesses-and-conditions/infections-and-poisoning/common-cold (accessed September 2020)

12. NHS. Flu. 2019. Available at: https://www.nhs.uk/conditions/flu/ (accessed September 2020)

13. World Health Organization. Q&A: influenza and COVID-19 — similarities and differences. 2020. Available at: https://www.who.int/westernpacific/news/q-a-detail/q-a-similarities-and-differences-covid-19-and-influenza (accessed September 2020)

14. Centers for Disease Control and Prevention. Cold versus flu. 2020. Available at: https://www.cdc.gov/flu/symptoms/coldflu.htm (accessed September 2020)

15. Anthony S., Fauci,MD. Influenza. - In: Harrison's PRINCIPLES OF INTERNAL MEDICINE 17th Edition 2008 by The McGraw-Hill Companies, Inc.

16. Beigel J, Bray M (April 2008). "Current and future antiviral therapy of severe seasonal and avian influenza". Antiviral Res. 78 (1): 91–102.

17. Bright RA, Medina MJ, Xu X, et al. (October 2005). "Incidence of HYPERLINK "http://priede.bf.lu.lv/grozs/Mikrobiologijas/Virusol/Raksti_2006/Gripa/Adamantana_rezist_gripa.pdf"adamantane HYPERLINK "http://priede.bf.lu.lv/grozs/Mikrobiologijas/Virusol/Raksti_2006/Gripa/Adamantana_rezist_gripa.pdf" resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern" (dead link). Lancet 366 (9492): 1175–81.

18. Bayer WH. Influenza B encephalitis. West J Med. 1987;147:466–468.

19. Boivin G, Hardy I, Tellier G, Maziade J. Predicting influenza infections during epidemics with use of a clinical case definition. Clin Infect Dis. 2000;31:1166–1169.

20. Arden NH, Patriarca PA, Kendal AP. Experiences in the use and efficacy of inactivated influenza vaccine in nursing homes. In: Kendal A, ed. Options for the Control of Influenza. Keystone, Colo: Liss; 1986:155–168.

21. Brankston G, Gitterman L, Hirji Z, Lemieux C, Gardam M (April 2007). "Transmission of influenza A in human beings". Lancet Infect Dis 7 (4): 257–65.

22. Capua, I; Alexander D (2006). "The challenge of avian influenza to the veterinary community". Avian Pathol 35 (3): 189–205.

23. Centers for Disease Control and Prevention, Atlanta, USA.”Antivirals with activity against influenza viruses are an important addition to the influenza vaccine to control influenza”. Electronically published in January 2013

24. Clements ML, Betts RF, Murphy BR. Advantage of live attenuated cold-adapted influenza A virus over inactivated vaccine for A/Washington/80 (H3N2) wild-type virus infection. Lancet. 1984;1:704–708.

25. Centers for Disease Control and Prevention. Prevention and control of influenza: Recommendations of the advisory committee on immunization practice. MMWR Morb Mortal Wkly Rep. 2003;52(RR-8):1–26.

26. Edelen JS, Bender TR, Chin TDY. Encephalopathy and pericarditis during an outbreak of influenza. Am J Epidemiol. 1974;100:79–83.

27. FREDERICK G. HAYDEN, P. PALESE. Influenza Virus. - In Douglas D. Richman, Richard J. Whitley, Frederick G. Hayden, Clinical virology 2002, 891- 920.

28. Gertsch J, Güttinger M, Sticher O, Heilmann J. (2002). "Relative quantification of mRNA levels in Jurkat T cells with RT-real time-PCR (RT-rt-PCR): new possibilities for the screening of anti-inflammatory and cytotoxic compounds". Pharm Res 19 (8)

29. Hurt AC, Ho HT, Barr I (October 2006). "Resistance to anti-influenza drugs: adamantanes and neuraminidase inhibitors". Expert Rev Anti Infect Ther 4 (5): 795–805.

30. JOHN J. TREANOR . Influenza Viruses, Including Avian Influenza and Swine Influenza. In: MANDELL, DOUGLAS, AND BENNETT'S PRINCIPLES AND PRACTICE OF INFECTIOUS DISEASES.2010; 2265-2288

31. Joyce C (2002). "Quantitative RT-PCR. A review of current methodologies". Methods Mol. Biol. 193: 83–92.

32. Kang XP, Jiang T, Li YQ, et al. (2010). "A duplex real-time RT-PCR assay for detecting H5N1 avian influenza virus and pandemic H1N1 influenza virus". Virol. J. 7: 113.

33. Livak KJ, Schmittgen TD (December 2001). "Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta HYPERLINK "http://linkinghub.elsevier.com/retrieve/pii/S1046-2023(01)91262-9"Delta HYPERLINK "http://linkinghub.elsevier.com/retrieve/pii/S1046-2023(01)91262-9" C(T)) Method". Methods (San Diego, Calif.) 25 (4): 402–8.

34. Mackay, Ian (2007). Real-time PCR in Microbiology: From Diagnosis to Characterization. Norfolk, England: Caister Academic Press. pp. 440.

35. Monto AS, Gravenstein S, Elliott M, et al. Clinical signs and symptoms predicting influenza infection. Arch Intern Med. 2000;160:3243–3247.

36. Peter F. W., Gabriele N., Yoshihiro K. Orthomyxoviruses. – In: Fields Virology, 5th Edition 2007.

37. Richman DD, Hostetler KY, Yazaki PJ, Clark S. Fate of influenza A virion proteins after entry into subcellular fractions of LLC cells and the effect of amantadine. Virology. 1986;151:200–210.

38. Rajeevan MS, Vernon SD, Taysavang N, Unger ER (February 2001). "Validation of array-based gene expression profiles by real-time (kinetic) RT-PCR". J Mol Diagn 3 (1): 26–31.

39. Newton DW, Mellen CF, Baxter BD, et al. Practical and sensitive screening strategy for detection of influenza virus. J Clin Microbiol. 2002;40:4353–4356.

40. Spackman E, Suarez DL (2008). "Type A influenza virus detection and quantitation by real-time RT-PCR". Methods Mol Biol 436: 19–26.

41. Scott A. Harper,1 John S. Bradley,2,3 et all. Seasonal Influenza in Adults and Children — Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management: Clinical Practice Guidelines of the Infectious Diseases Society of America . electronically published 12 March 2009.

42. WHO Library Cataloguing-in-Publication Data. Manual for the laboratory diagnosis andvirological surveillance of influenza. 2011

43. Wright Peter: Influenza Viruses. - In Nelson Textbook of Pediatrics, 19th ed. 2011.

44. WHO Guidelines for Pharmacological Management of Pandemic Influenza A(H1N1) 2009 and other Influenza Viruses". Revised February 2010